IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

App. No.	:	10/820,656	Confirmation No. 8010
Applicants	:	Schaub, Robert G., et al.	
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Examiner	:	Alstrum-Acevedo, J.H.	
Docket No.	:	31176282-004001	
Customer No.	:	51738	
Entitled	:	Hemophilia Treatment by Inhalation of Coagulation Factors.	

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICE ACTION MAILED JULY 27, 2006
PURSUANT TO 37 C.F.R. § 1.116

Dear Sir:

In response to the Final Office Action dated July 27, 2006, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

I. AMENDMENTS TO THE CLAIMS

There are no amendments to the claims.

Listing of Claims:

Claim 1 (original) A method of treating hemophilia, said method comprising

a) aerosolizing a Factor IX (F.IX), wherein the aerosolized F.IX:

i) has a mass median aerodynamic diameter (MMAD) of between 2 and 4 μm, has a fine particle fraction percent less than 3.3 μm (FPF%<3.3 μm) of at least 50%,

ii) is at least 90% monomeric,

iii) wherein the after-aerosolization activity/pre-aerosolization activity is at least 80%; and

iv) is a dry powder having less than 10% water (wt/wt);

b) inhaling the aerosolized F.IX and allowing the aerosolized F.IX to deposit in the lung;

c) followed by exhalation.

Claim 2 (original) The method of claim 1, wherein the MMAD is 2.8 to 3.6 μm, the FPF%<3.3 μm is at least 60%, the monomer content is at least 95% and the after-aerosolization activity/pre-aerosolization activity is at least 90%.

Claim 3 (original) The method of claim 1, wherein the MMAD is about 3-3.5 μm, the FPF%<3.3 μm is at least 64%, the monomer content is at least 97%, and the after-aerosolization activity/pre-aerosolization activity is at least 95%.

Claim 4 (original) The method of claim 1, wherein the F.IX is aerosolized without alcohol.

Claim 5 (original) The method of claim 1, wherein the F.IX is recombinant.

Claim 6 (original) The method of any of claims 1 through 5, wherein the F.IX comprises a tri-leucine excipient.

Claim 7 (original) The method of claim 6, wherein the tri-leucine/F.IX ratio is 0.5-1.5wt/wt.

Claim 8 (original) A method of treating hemophilia, said method comprising the inhalation of aerosolized, dry Factor IX (F.IX), wherein the aerosolized dry F.IX:

a) comprises a surface active di- or tri-peptide, b) has a MMAD of between 2.8-3.5 μm, c) an FPF%<3.3 μm of greater than 60%, d) a monomer content of at least 95%, e) the after-aerosolization activity/pre-aerosolization activity is at least 80%, and f) less than 10% water.

Claim 9 (original) The method of claim 8, wherein the MMAD is about 3-3.5 μm, the FPF%<3.3 μm is at least 64%, the after-aerosolization activity/pre-aerosolization activity is at least 90%; the monomer content is at least 97% and the water content is less than 5%.

Claim 10 (original) The method of claim 8, wherein the F.IX does not contain alcohol.

Claim 11 (original) The method of claim 8, wherein the F.IX is recombinant.

Claim 12 (original) The method of any of claims 8 through 11, wherein the F.IX comprises a tri-leucine excipient.

Claim 13 (original) The method of claim 6, wherein the tri-leucine/F.IX ratio is 0.5-1.5wt/wt.

Claim 14 (original) A method of preventing hemophilic bleeding in advance of a hemophilic assault, said method comprising

a) aerosolizing a Factor IX (F.IX), wherein the aerosolized F.IX:

i) has a mass median aerodynamic diameter (MMAD) of between 2 and 4 μm,

ii) has a fine particle fraction percent less than 3.3 μm (FPF%<3.3 μm) of at least 50%,

iii) is at least 90% monomeric,

iv) wherein the after-aerosolization activity/pre-aerosolization activity is at least 80%; and

v) is a dry powder having less than 10% water (wt/wt);

b) inhaling the aerosolized F.IX at least once per week and allowing the aerosolized F.IX to deposit in the lung;

c) followed by exhalation.

Claim 15 (original) The method of claim 14, wherein the inhalation is bi-weekly.

Claim 16 (original) The method of claim 14, wherein the inhalation is every 2 to 3 days.

Claim 17 (original) A composition comprising aerosolizable dry F.IX having, when aerosolized an MMAD between 2 and 4 μm, an FPF%<3.3 μm of at least 50%, an emitted dose (ED) of at least 50%, a monomer content of at least 95%, wherein the after-aerosolization activity/pre-aerosolization activity is at least 80%, less than 10% water, and a surface active di- or tri-peptide excipient, but does not have ethanol.

Claim 18 (original) The composition of claim 17, wherein the MMAD is between 2.8 and 3.6 μm, the ED is at least 60%, the after-aerosolization activity/pre-aerosolization activity is at least 95%, the FPF%<3.3 μm is at least 65% and less than 5% water.

Claim 19 (original) The composition of claim 17, wherein the MMAD is between 3 and 3.5 μm, the FPF%<3.3 μm is at least 64%, the ED is at least 80%, wherein the after-aerosolization activity/pre-aerosolization activity is at least 95%, the monomer content is at least 97% and the water content is less than 5%.

Claim 20 (original) A blister pack containing F.IX, wherein the blister pack is waterproof and contains F.IX that is at least 90% monomeric and has less than 10% (wt/wt) water and a surface active di- or tri-peptide excipient, but does not have ethanol.

Claim 21 (original) The blister pack of claim 20, wherein the F.IX is at least 95% monomeric and has less than 5% (wt/wt) water and the excipient is a dileucyl or a tri-leucine.

Claim 22 (original) The blister pack of claim 20, wherein the F.IX is at least 97% monomeric and has less than 5% (wt/wt) water and the excipient is tri-leucine.

Claim 23 (original) The blister pack of any of claims 20 to 22, wherein the F.IX is recombinant F.IX.

Claim 24 (original) A dry powdered F.IX comprising a biologically active recombinant Factor IX that is at least 90% monomeric and has less than 10% water, and a surface active di- or tri-peptide excipient, but does not have ethanol.

Claim 25 (original) The dry powdered F.IX of claim 24, wherein the excipient is tri-leucine.

Claim 26 (original) The dry powdered F.IX of claim 25, wherein there ratio of F.IX to excipient is 0.2-5.0/1.

Claim 27 (original) A composition comprising dry, dispersible powder and a solid content of about 50 wt% glycosylated F.IX, about 40 wt% trileucine and about 10 wt% buffer.

Claim 28 (original) A composition comprising dry, dispersible powder and a solid content of 40-60 wt% glycosylated F.IX, 40-60 wt% trileucine and 0-10 wt% buffer.

REMARKS

The claims have been twice rejected and are ripe for appeal. Applicants request reconsideration of the final rejection of claims 1-28 in this Response for the reasons stated below.

Sequestration of F.IX not disclosed

Claims 14-16 are directed to "methods of treating hemophilia **in advance**" comprising inhalation "once a week." The application specifically states that monomeric F.IX is sequestered allowing for a bi-weekly treatment which lasts 2-4 days (¶22). Prior intravenous treatments were more rapidly cleared from the blood, thus a **weekly or bi-weekly** prophylactic treatment would not have been possible (Fig. 8). The sequestration and prophylactic treatment using F.IX was not disclosed, nor predictable from the Lechuga reference. One of ordinary skill in the art would not have the teaching or motivation to treat hemophilia in advance with an inhalable F.IX composition. Claims 14-16 are non-obvious in light of Lechuga.

The sequestration effect offered by monomeric F.IX is an **unexpected result** obtained with the present invention. Thus, even if the *prima facie* obviousness case were met (and it is not), claim 14 *et seq* recite the entirely unexpected result of being able to treat hemophilia "in advance" of a bleeding episode due to this surprising sequestration effect and the case is rebutted. Therefore, claims 14 *et seq* (at least) are believed to be allowable and Applicants respectfully requests same.

Rejection of the claims 1-4, 6-10, 12-16, 18, 19, 21, 22, 24 under 35 U.S.C. §103(a) as being unpatentable over the Lechuga Application

The Lechuga application fails to establish a *prima facie* case of obviousness against claims 1-28 because it does not teach or suggest each and every element of the claimed invention.

1. Lechuga fails to disclose "monomeric"

As previously stated in the Response filed May 22, 2006. There is no teaching or suggestion in the Lechuga application regarding "at least 90% monomeric." Please see the Remarks on page 6 of the Response filed May 22, 2006. Monomer content below 80% was inactive and monomer content above 90% was required for activity. The conditions required to achieve and maintain *in vivo* activity are not disclosed in the Lechuga application. While native F.IX may be monomeric *in vivo*, there is **no reason to expect** it to remain monomeric and active when formulated as a dry powder!

2. Lechuga fails to disclose "FPF%<3.3 μm of at least 50%"

There is no teaching or suggestion in the Lechuga application regarding "a fine particle fraction percent less than 3.3 μm (FPF%<3.3 μm) of at least 50%." The Lechuga reference is silent regarding the fine particle fraction required for *in vivo* activity. FPF%<3.3 is directly related to ED and is essential for *in vivo* activity. Thus, the activity and conditions required for *in vivo* activity are not disclosed in the Lechuga application.

3. Lechuga fails to disclose "less than 10% water"

There is no teaching or suggestion in the Lechuga application regarding "a dry powder having less than 10% water (wt/wt)." The Lechuga reference is silent regarding the water content in F.IX preparations. Water content is directly related to F.IX storage and subsequent activity *in vivo*. Thus, the Lechuga application fails to disclose the storage conditions required to maintain *in vivo* F.IX activity.

Rejection of the claims 5-7, 11-13, and 23 under 35 U.S.C. §103(a) as being unpatentable over the Lechuga in view of Russell

The Lechuga application in view of Russell fails to establish obviousness against claims 1-28 because it does not teach or suggest each and every element of the claimed invention. Lechuga does not disclose "monomeric," "FPF%<3.3 μm of at least 50%," or "less than 10% water." Russell discloses intratracheal administration of liquid F.IX. Although Russell provides a "proof of concept" that F.IX can be delivered intratracheally, Russell fails to provide compositions required to achieve and maintain *in vivo* activity of aerosolized F.IX.

Rejection of the claims 1-4, 6-10, 12-16, 18, 19, 21, 22, and 24 under 35 U.S.C. §103(a) as being unpatentable over the Lechuga in view of DeFrees

The Lechuga application in view of DeFrees fails to establish obviousness against claims 1-28 because it does not teach or suggest a each and every element of the claimed invention. Lechuga does not disclose "monomeric," "FPF%<3.3 μm of at least 50%," or "less than 10% water." DeFrees discloses PEG derivatized peptides to reduce immunogenicity (PEG-ylation). Reduced immunogenicity through PEG-ylation does not address limitations in the current claims. DeFrees does not provide compositions required to achieve and maintain *in vivo* activity of aerosolized F.IX.

Obviousness-type Double Patenting of claims 17-19 over USSN 10/313,343 in view of Platz

US Application No. 10/313,343, now US Patent 6,372,258 (the '258 patent), is the US Counterpart of PCT Application WO 01/32144. The disclosure of the '258 patent is identical to the Lechuga application. Analysis of Obviousness-type Double Patenting as described in MPEP §804.B(1) requires (A) Determine the scope and content of a patent claim; (B) Determine the differences between the scope and content of the patent claim; (C) Determine the level of ordinary skill in the pertinent art; and (D) Evaluation of objective indicia of nonobviousness.

The '258 patent discloses tri-leucine solutions with F.IX, but does not disclose the requirements of aerosolized F.IX for *in vivo* activity. The '258 patent does not disclose "monomeric," "FPF%<3.3 μm of at least 50%," or "less than 10% water" as described in detail above for the Lechuga application. US 6,835,372 ("Platz") discloses optimizing MMAD for dried solutions. Platz complements the '258 patent with a method for generating aerosol solutions with a given MMAD. Platz and the '258 patent do not disclose "monomeric," "FPF%<3.3 μm of at least 50%," or "less than 10% water" used to achieve *in vivo* activity as described in the current application. Further, neither citation teaches that F.IX can be sequestered, allowing **treatment in advance by weekly or biweekly dosing**. Therefore, the '258 alone or in combination with Platz does not render the claims obvious.

Obviousness-type Double Patenting of claims 17-19 over USSN 10/985,509 in view of Platz

US Application No. 10/985,509 (the '509 application) is a continuation of the '258 patent and has an identical disclosure. Therefore it fails to render the claims obvious for the same reasons.

CONCLUSION

The present invention provides a "needle-free" hemophilia treatment with an extended prophylactic effect. Compositions that maintain F.IX activity during aerosol administration are required to achieve an effective treatment. The present invention achieves an F.IX composition that is active *in vivo* and maintains activity after storage.

The Lechuga applications (the PCT application, '258 patent, and the '509 application) do not disclose the same compositions as the present application. The Lechuga application fails to disclose the conditions required for *in vivo* activity and compositions that maintain *in vivo* activity during storage. None of the cited documents provide a method of treating hemophilia with an aerosolized F.IX that i) has a mass median aerodynamic diameter (MMAD) of between 2 and 4 μm, has a fine particle fraction percent less than 3.3 μm (FPF%<3.3 μm) of at least 50%, ii) is at least 90% monomeric, iii) wherein the after-aerosolization activity/pre-aerosolization activity is at least 80%; and iv) is a dry powder having less than 10% water (wt/wt). This F.IX composition is unique in that it achieves activity *in vivo*, maintains activity *in vivo* after storage, and is sequestered in the lungs for a prolonged period of time.

The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 50-3420(reference 31176282-004001 MDB).

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Respectfully submitted,

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